(45 min)

Alcoholic Liver Disease:

Pathophysiology, Treatment, and Challenges

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National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health

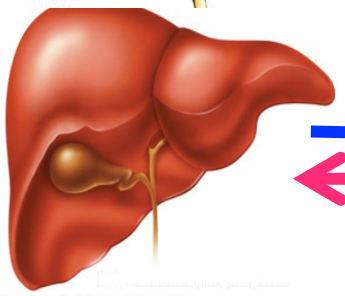
U.S. Department of Health and Human Services

Alcoholic Liver Disease

Alcohol

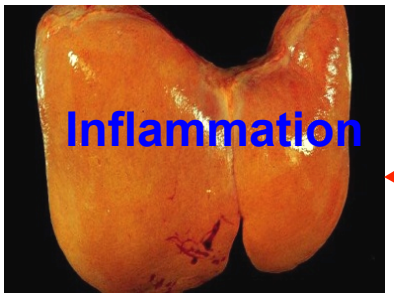
Acute (sub-acute) Alcoholic Hepatitis

Clinical syndrome: Jaundice, hepatomegaly, fever, Neutrophilia, AST: ALT ratio>2



Fatty Liver

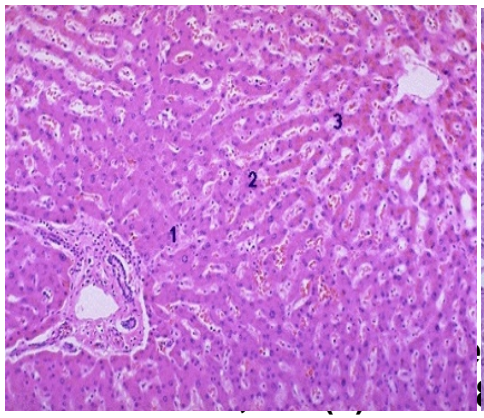
30-40%

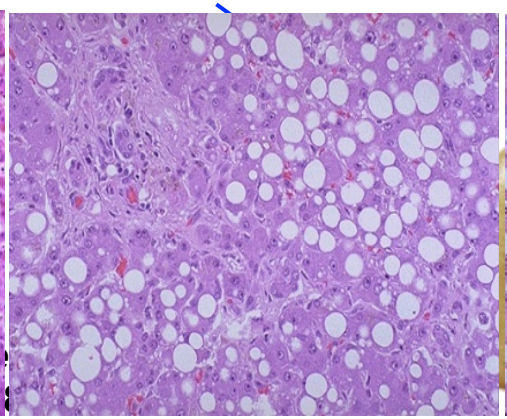


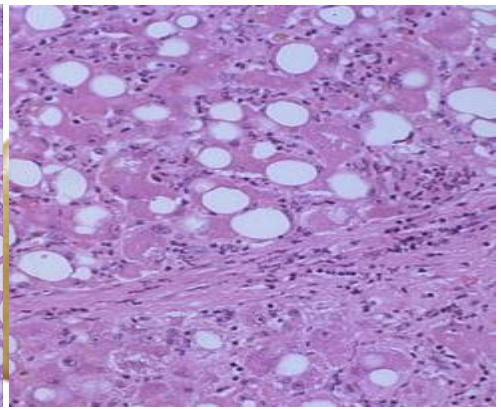
Alcoholic Steatohepatitis (ASH)

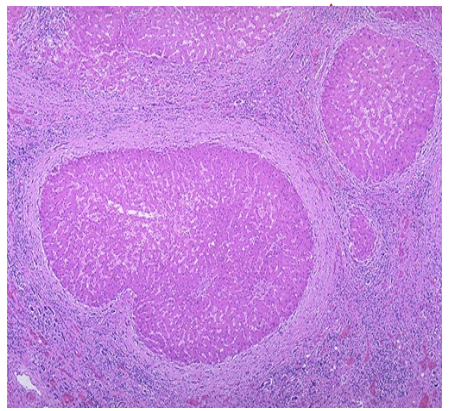
10-20%

Cirrhosis



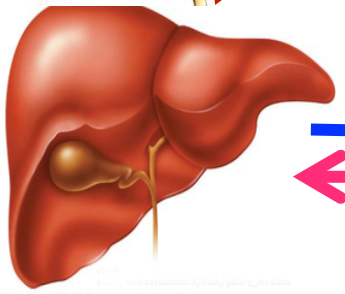






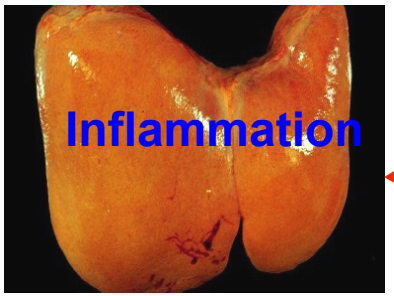
How is ethanol metabolized in the liver?

Alcohol



Fatty Liver

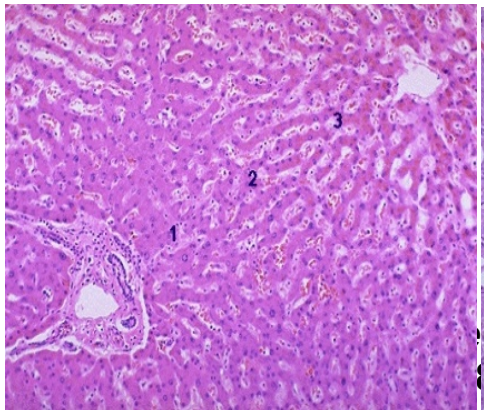
30-40%

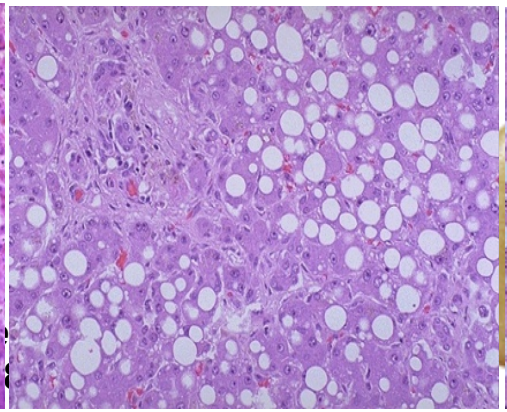


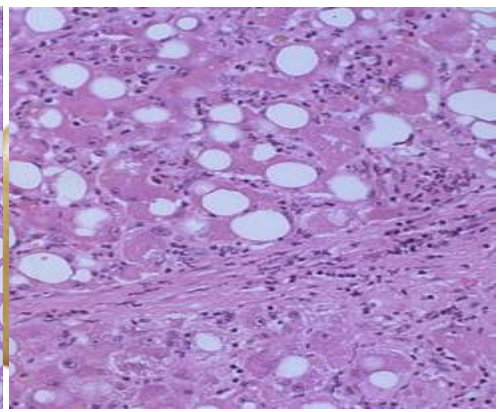
Alcoholic Steatohepatitis (ASH)

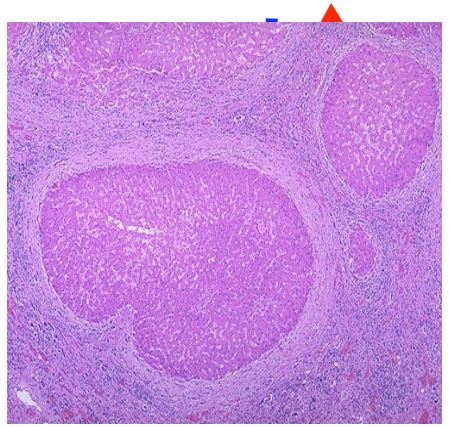
10-20%

Fibrosis
Cirrhosis



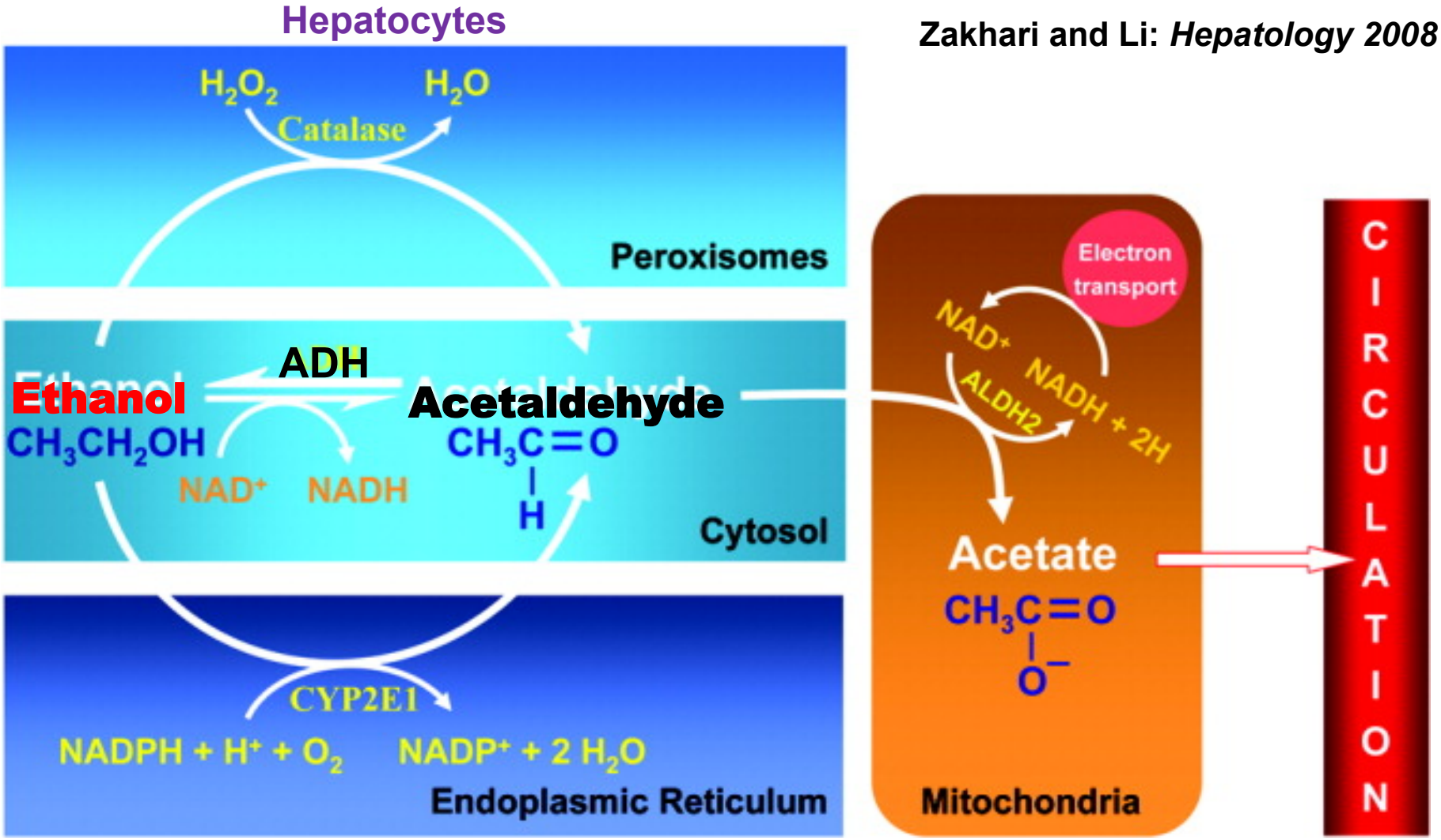




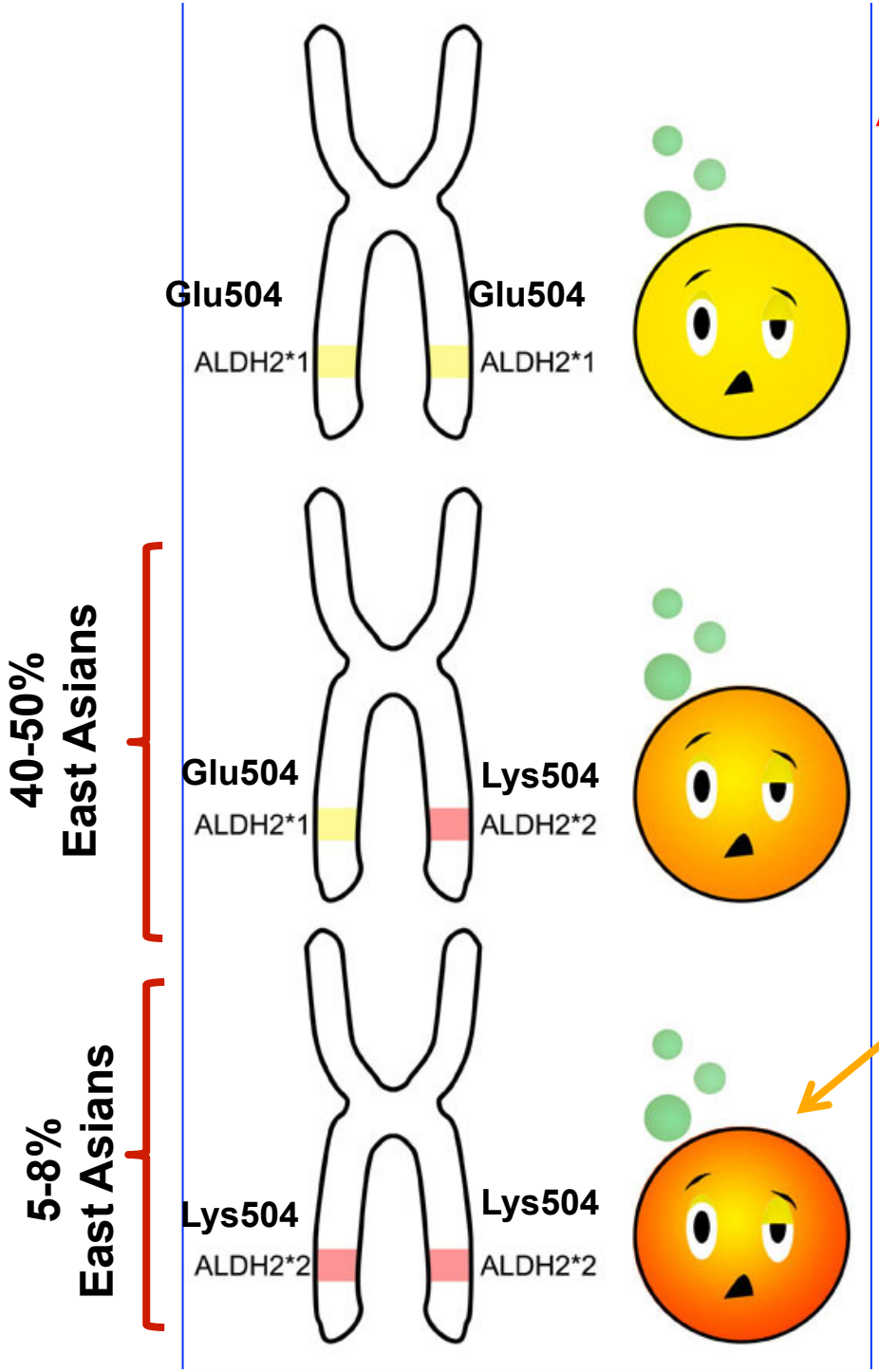


Oxidative Pathways of Alcohol Metabolism

Zakhari and Li: *Hepatology 2008*



ADH: Alcohol Dehydrogenase; ALDH2: Aldehyde Dehydrogenase 2;
CYP2E1: cytochrome P450 2E1; NAD+: oxidized nicotinamide adenine dinucleotide;
NADH: reduced nicotinamide adenine dinucleotide;
NADP+: oxidized nicotinamide adenine dinucleotide phosphate;
NADPH: reduced nicotinamide adenine dinucleotide phosphate



ALDH2:
Aldehyde Dehydrogenase 2 polymorphism

Glu504 homozygotes (*ALDH2*1/1*) exhibit normal enzymatic activity to metabolize acetaldehyde

Acetaldehyde → Acetate

Glu504/Lys504 heterozygotes (*ALDH2*1/2*) show approximately 6% of normal activity,

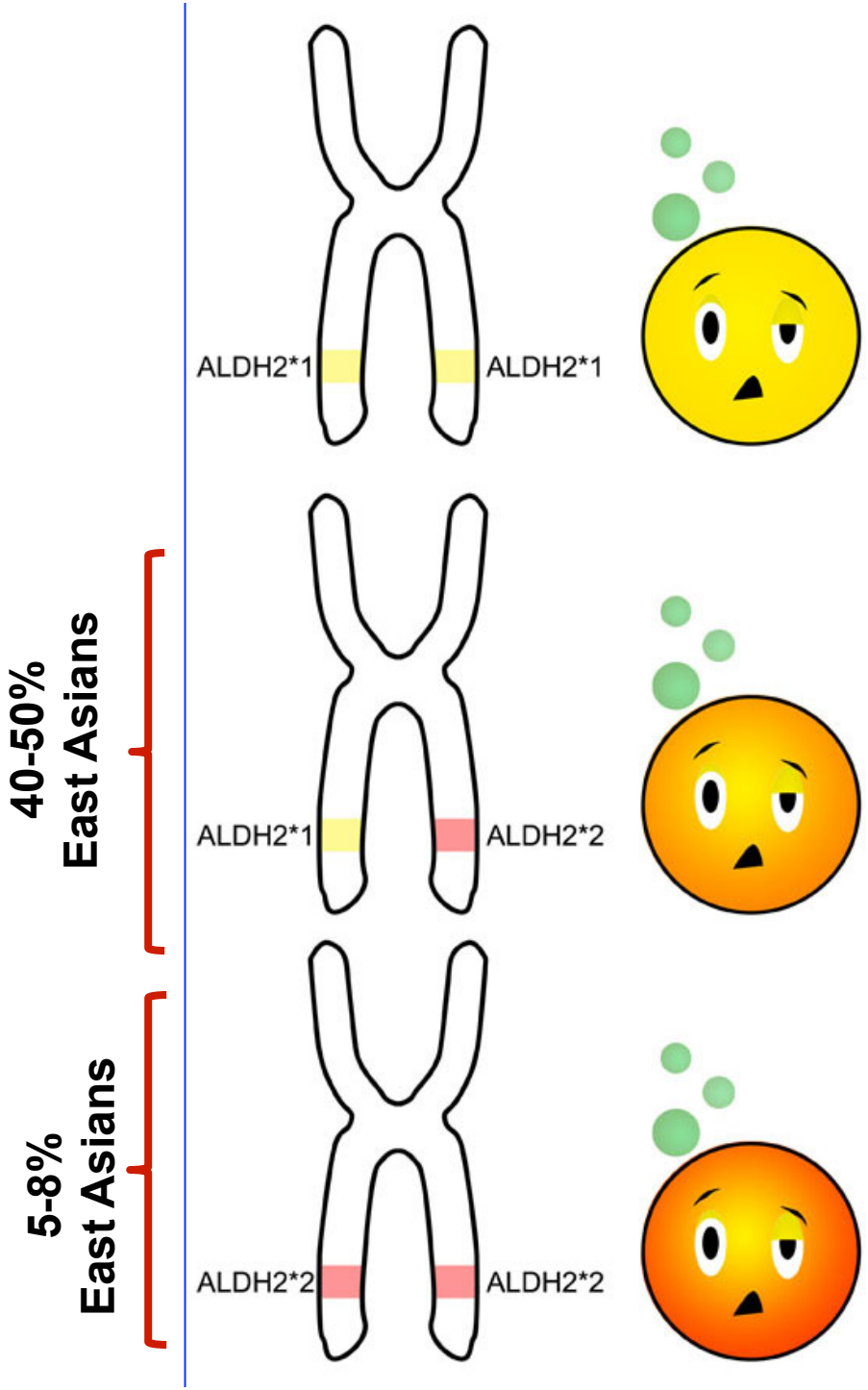
Lys504 homozygotes (*ALDH2*2/2*) show negligible activity toward acetaldehyde

↑ Acetaldehyde ----→ Acetate

↓

Flushing

ALDH2:
Aldehyde Dehydrogenase 2 polymorphism



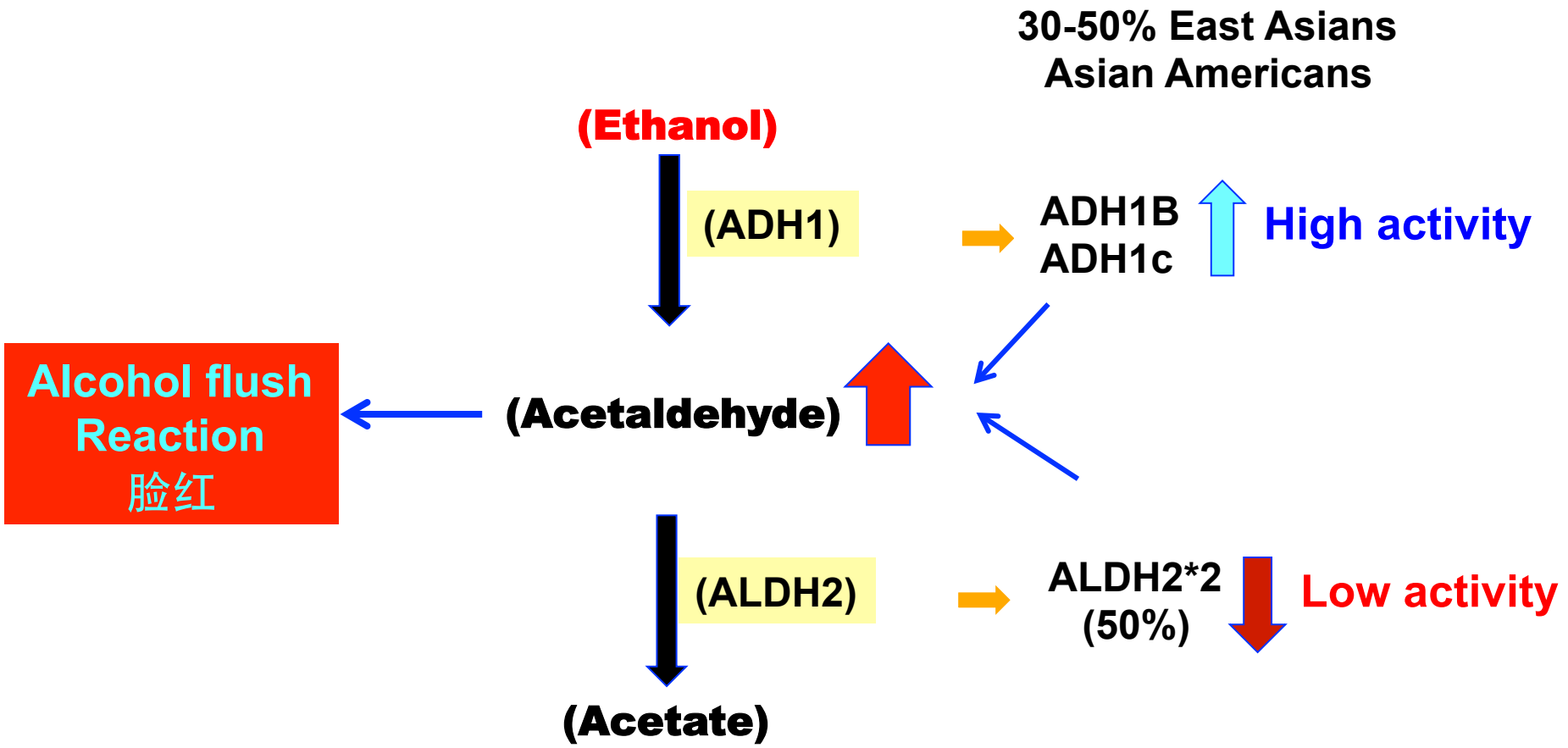
Alcoholic liver disease in patients with this genotype has been extensively characterized in Western countries.

Alcoholic liver disease in patients with ALDH2 deficiency has not been characterized, which may be very different from the patients with ALDH2*1/1

One of major projects in our lab at NIAAA

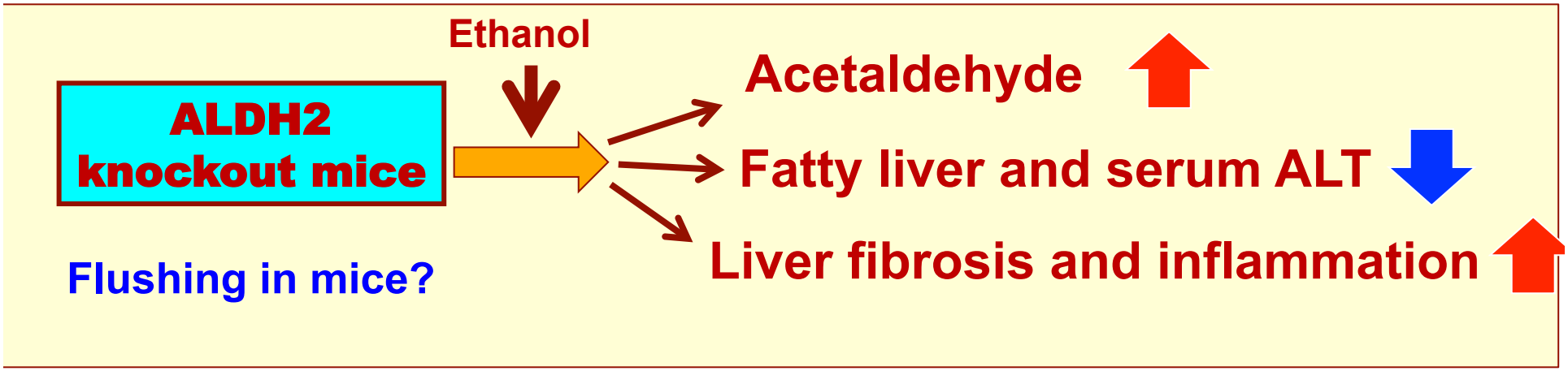
The 1st International symposium in Shanghai in 2016

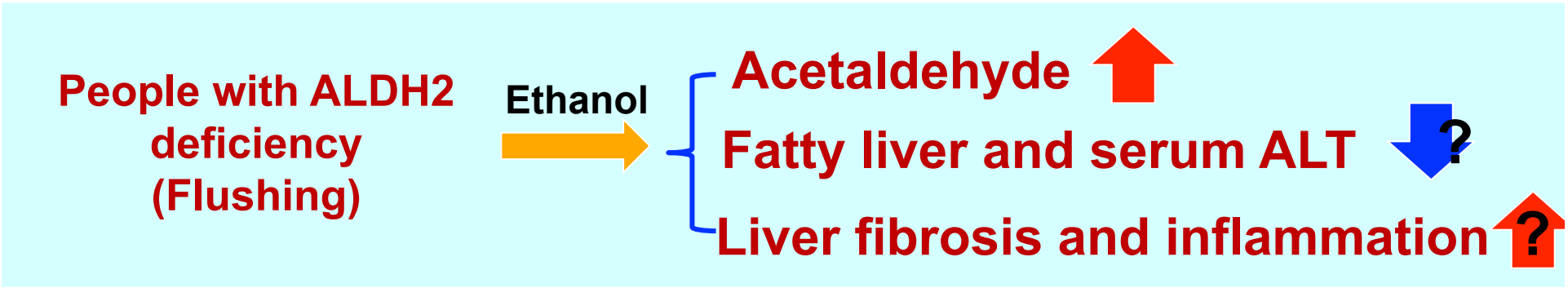
Ethanol metabolism in East Asians , Asian Americans



Are individuals who have alcohol flushing reaction more susceptible to alcoholic liver injury and inflammation?

Kwon HJ Won YS Park O Chang B Duryee MJ Thiele G Matsumoto A Singh S Abdelmegeed M Song B Kawamoto T Vasiliou V Thiele G Gao B *Hepatology* 2014 Jul;60(1):146-57.



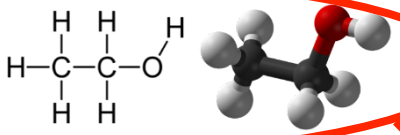


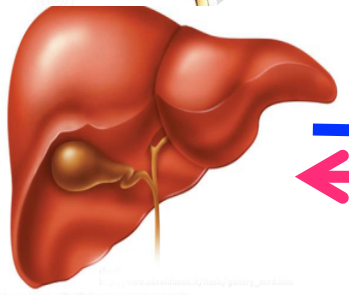
How is ethanol metabolized in the liver?

How does ethanol cause liver injury?

Alcohol

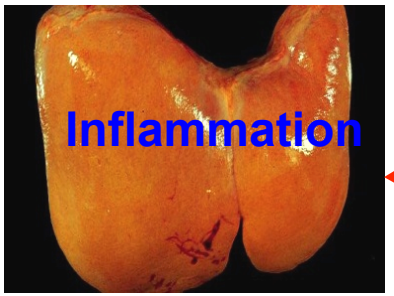
Ethanol





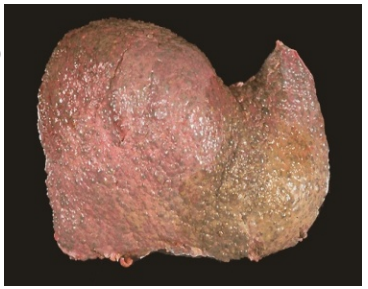
Fatty Liver

30-40%

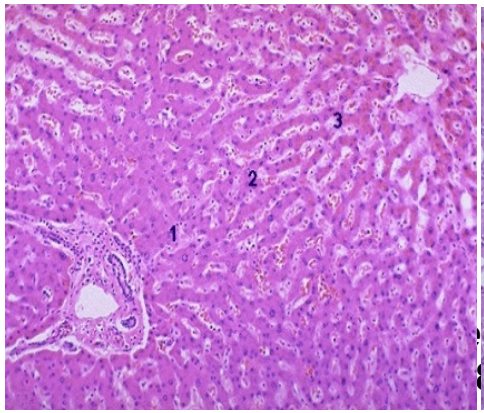


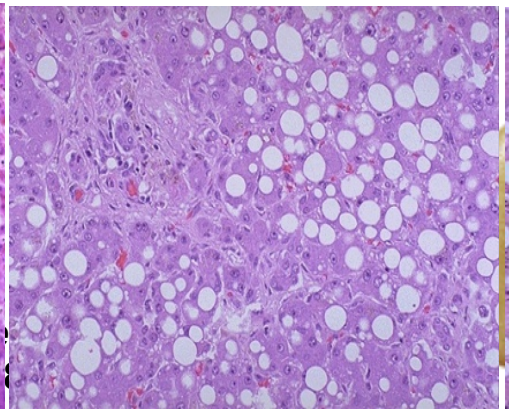
Alcoholic Steatohepatitis (ASH)

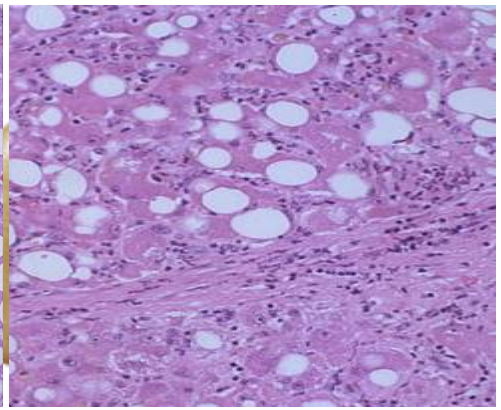
10-20%

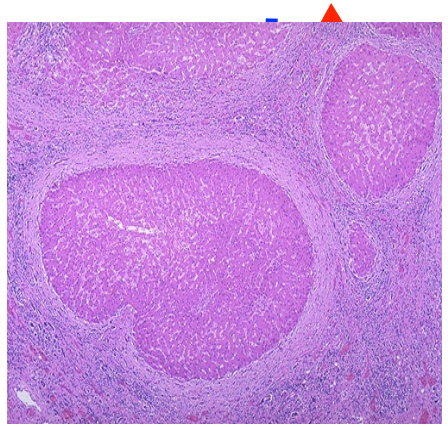


Fibrosis
Cirrhosis







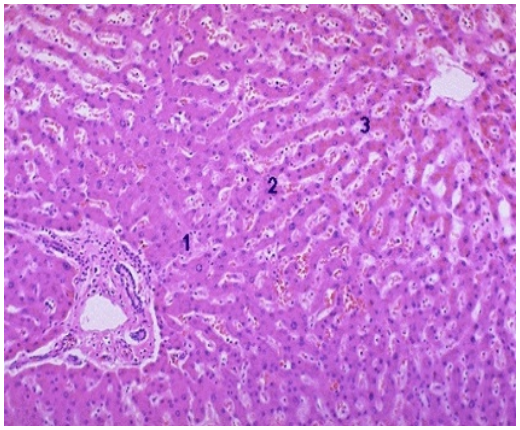


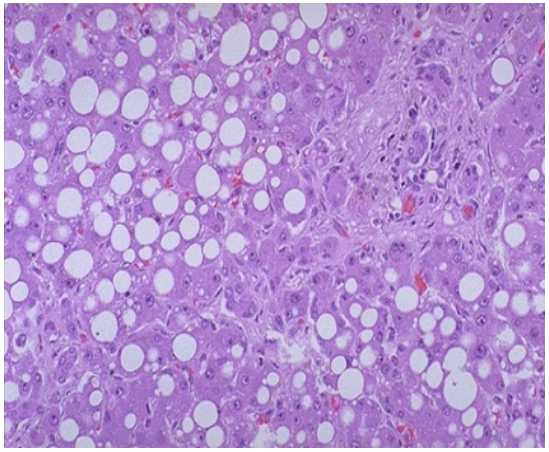
Molecular Mechanisms of *Alcoholic Fatty Liver*

a. Ethanol metabolites do not contribute directly to fat synthesis

b. Ethanol leads to fatty liver via dysregulating fat metabolism

Alcohol, its metabolites, its metabolism-associated oxidative stress promote fat synthesis and inhibit fatty acid β oxidation





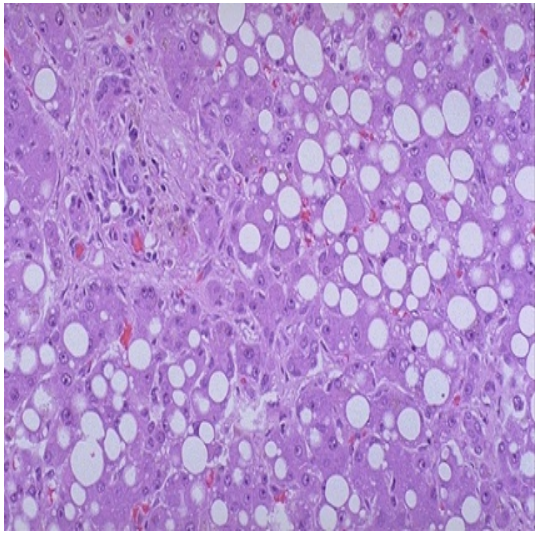
Purohit, Gao, Song. Molecular mechanisms of alcoholic fatty liver. *Alcohol Clin Exp Res.* 2009, 33:191-205

Gao and Bataller. Alcoholic liver disease: Pathogenesis and therapeutic targets. *Gastroenterology* 2011, 141:1572-85

Molecular Mechanisms of *Alcoholic Steatohepatitis*

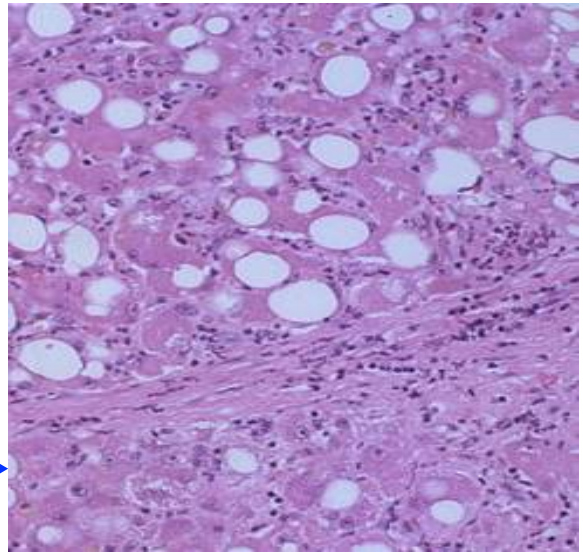
Inflammation

Alcohol



Gut bacterial
Dysbiosis
Gut permeability
Oxidative stress
Lipid peroxidation

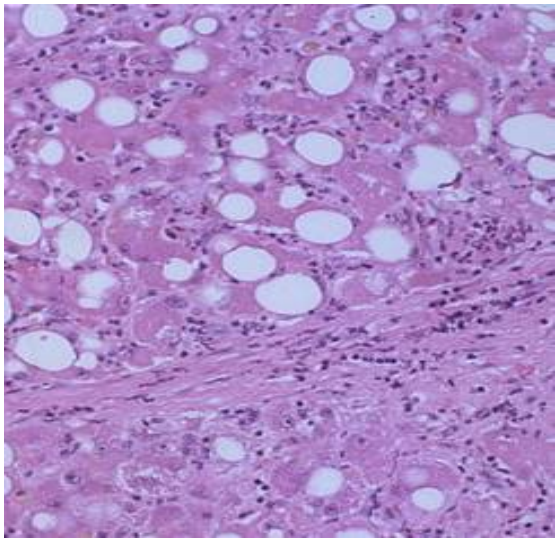
Endotoxin
Cytokines
Oxidative
stress



Gao and Bataller. Alcoholic liver disease: Pathogenesis and therapeutic targets. *Gastroenterology* 2011, 141:1572-85

Molecular Mechanisms of *Alcoholic Cirrhosis*

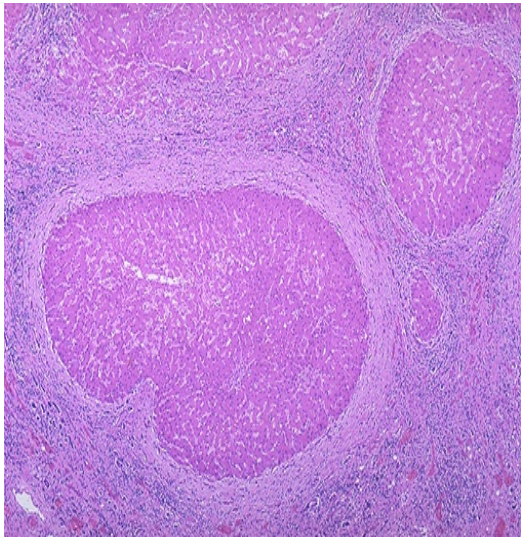
Cirrhosis **is a slowly progressing disease in which healthy** ***liver*** **tissue is replaced with scar tissue that is mainly produced by activated hepatic stellate cells**



Alcohol

Alcohol
Acetaldehyde
Oxidative stress
Cytokines

Stellate cell activation



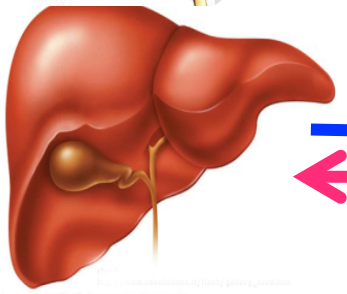
Gao and Bataller. Alcoholic liver disease: Pathogenesis and therapeutic targets. *Gastroenterology* 2011, 141:1572-85

How is ethanol metabolized in the liver?

How does ethanol cause liver injury?

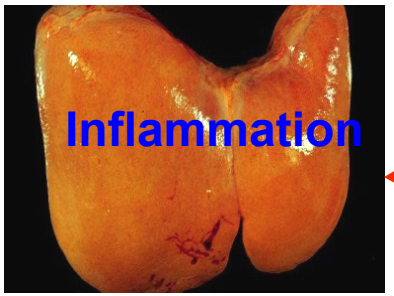
Alcohol

Only 30-40% of heavy drinkers develop more severe forms of ALD, such as advanced ASH, fibrosis and cirrhosis.



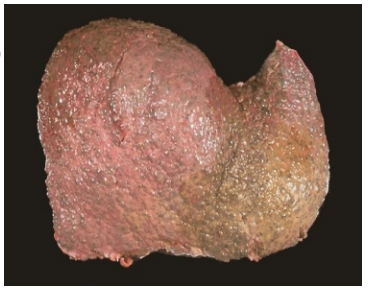
Fatty Liver

30-40%



Alcoholic Steatohepatitis (ASH)

10-20%



Fibrosis
Cirrhosis

1-3%
per year

60-70%

Fatty Liver

Gao and Bataller, *Gastroenterology* 2011, 141(5):1572-85

Only 30-40% of heavy drinkers develop more severe forms of ALD, such as advanced ASH, fibrosis and cirrhosis.

Many genetic and acquired factors are involved:

- Nutritional factors
- The dose and duration of alcohol consumption
- Drinking Pattern
- Age of onset of drinking
- Genetic polymorphisms of cytokines and alcohol-metabolizing enzymes
- Gender
- Immunologic factors
- Genetic predisposition to alcohol addiction
- Hepatic iron overload
- Comorbidity (viral hepatitis, obesity, diabetes etc.)

Gao and Bataller. Alcoholic liver disease: Pathogenesis and therapeutic targets. *Gastroenterology* 2011, 141:1572-85

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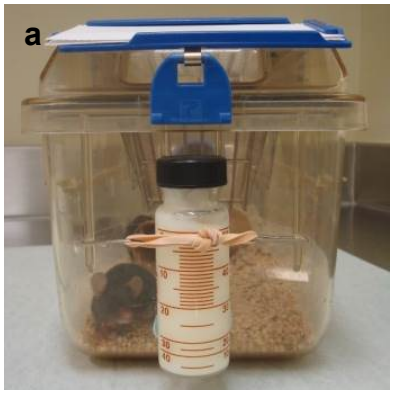
Nature Protocols 2013

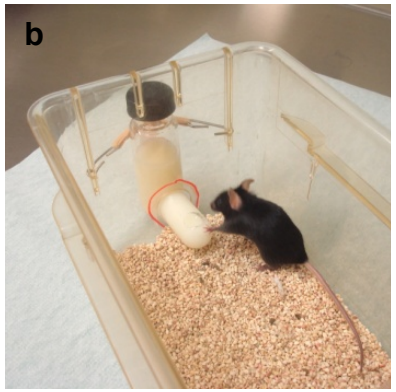
Mouse model of chronic and binge ethanol feeding (the NIAAA model)

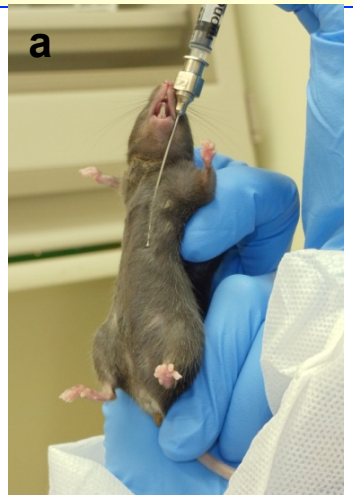
Adeline Bertola, Stephanie Mathews, Sung Hwan Ki, Hua Wang & Bin Gao

Laboratory of Liver Diseases, National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institutes of Health (NIH), Bethesda, Maryland, USA.
Correspondence should be addressed to B.G. (bgao@mail.nih.gov).

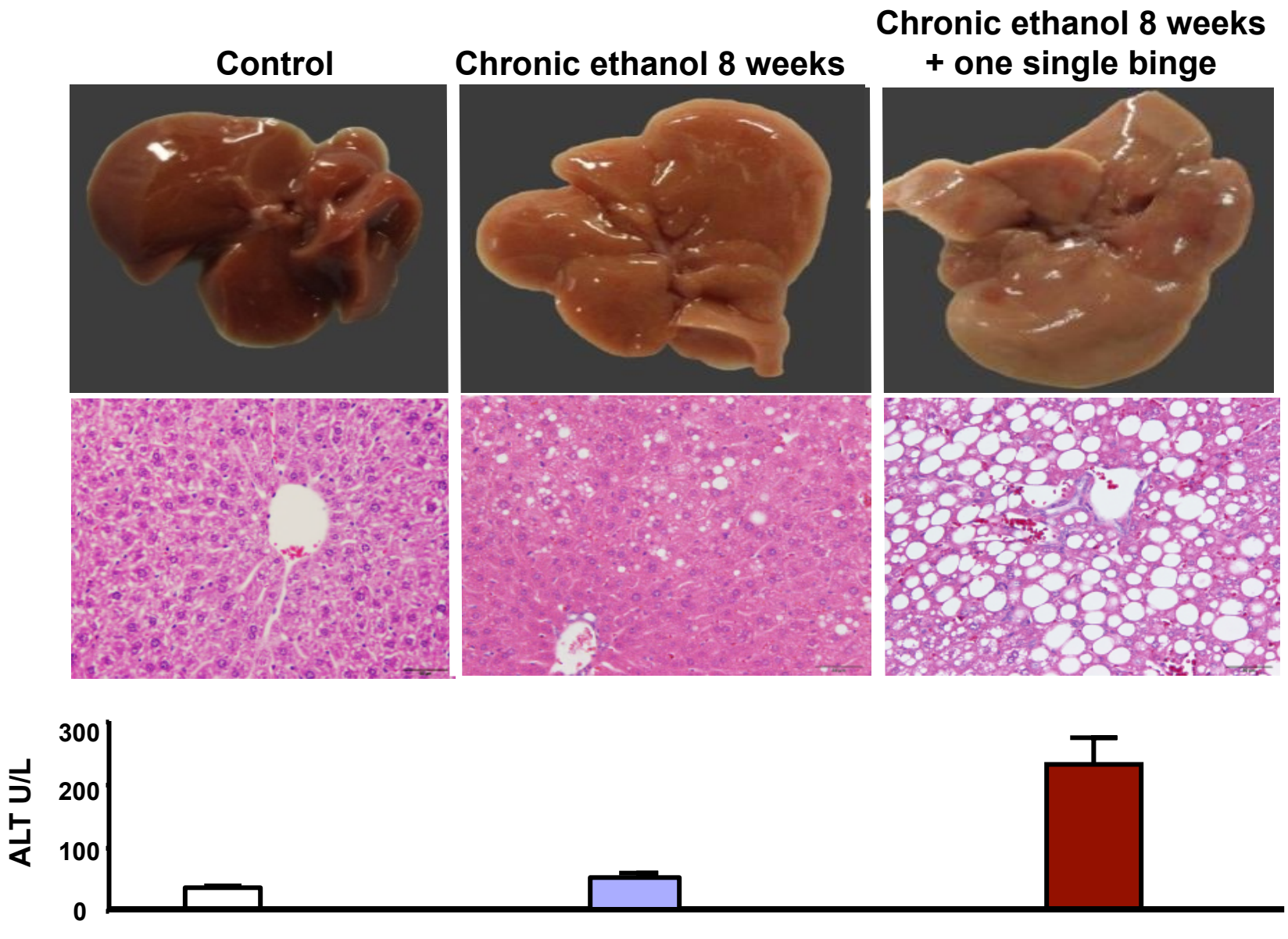
Chronic feeding + **Binge** → **Alcoholic Hepatitis**







Chronic-plus-binge ethanol feeding induces severe liver injury



Alcohol and Obesity

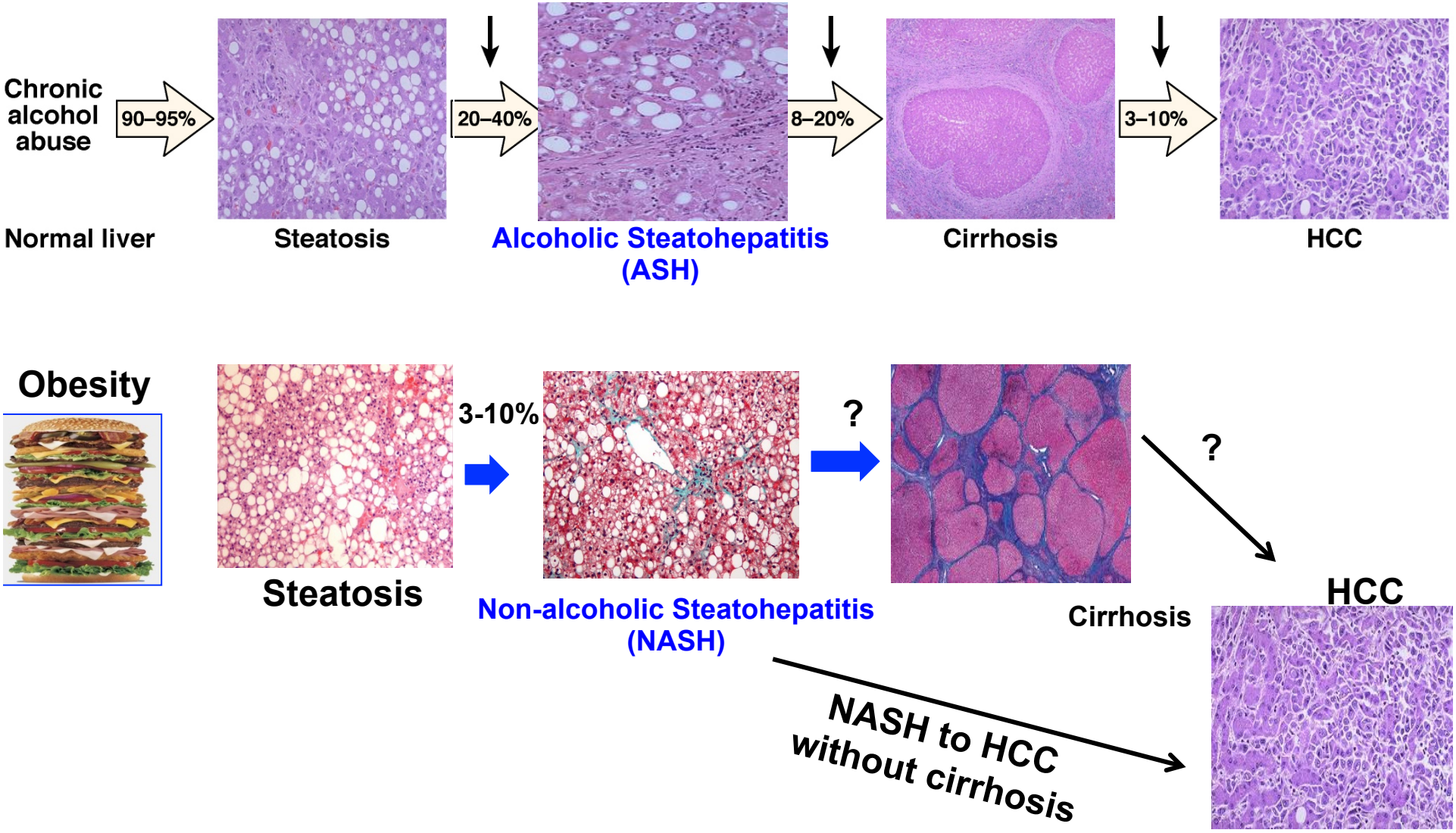
Alcohol Use and Obesity in the United States

More than two-thirds of U.S. adults are overweight or obese

Prevalence of Drinking: In 2012, 87.6% of people ages 18 or older reported that they drank alcohol at some point in their lifetime; 71% reported that they drank in the past year; 56.3% reported that they drank in the past month.

How does the interaction of alcohol and fat affect the liver?

Spectrum of Alcoholic Liver Disease (ALD) and Non-alcoholic Fatty Liver Disease (NAFLD)



Alcoholic liver disease (ALD): diagnosis

ALD diagnosis is based on:

- A past and present history of significant alcohol drinking (Man: ≥20-30 g/d; Women: ≥14 g/d)
- Clinical evidence of liver disease
- Elevation of serum AST and ALT (AST/ALT>2)
- Serum AST is elevated to a level of 2-6 times the upper limits of normal in severe alcoholic hepatitis.
- AST/ALT ratio > 3 is highly suggestive of ALD

Robert S. O'Shea, Srinivasan Dasarathy, Arthur J. McCu
Alcoholic liver disease (AASLD guideline)
Hepatology 2010

Nonalcoholic fatty liver disease (NAFLD): diagnosis

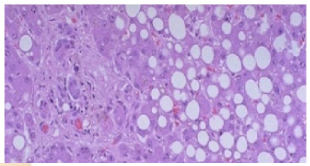
NAFLD diagnosis :

- The diagnosis of NAFLD requires: hepatic steatosis (exclude other causes of hepatic fat accumulation)
- In the majority of patients, NAFLD is associated with metabolic risk factors such as obesity, diabetes mellitus, and dyslipidemia.
- NAFLD is histologically further categorized into
  Nonalcoholic fatty liver (NAFL)
  Nonalcoholic steatohepatitis (NASH)
- Elevation of serum AST and ALT (AST/ALT<1)

Spectrum of Alcoholic Liver Disease (ALD) and Non-alcoholic Fatty Liver Disease (NAFLD)

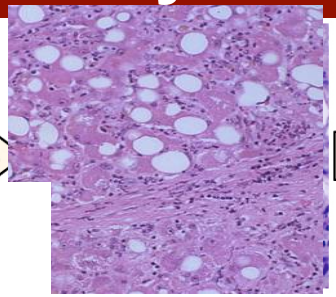
Chronic alcohol

90–95%



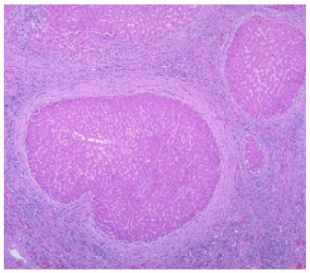
Steatosis

20–40%



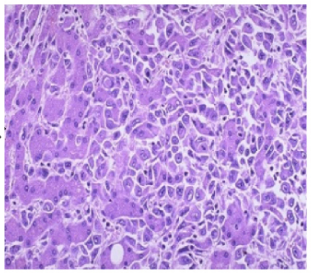
olic Steatohepatitis (ASH)

8–20%



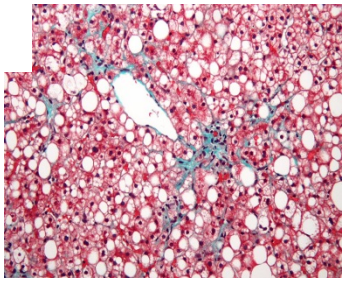
Cirrhosis

3–10%

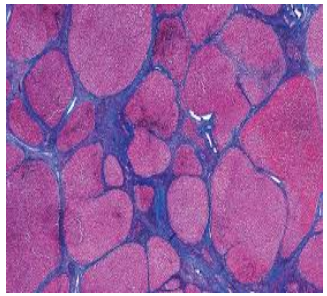


HCC

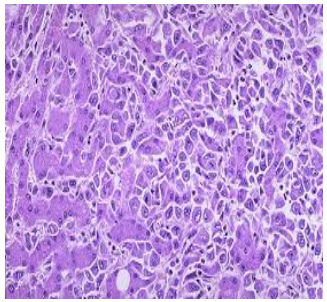
3-10%



Non-alcoholic Steatohepatitis (NASH)



Cirrhosis



HCC

Obesity and alcohol contribute to the pathogenesis of fatty liver disease. How much for each of them?

How to distinguish ALD and NAFLD? ANI

Mayo clinic: The Alcoholic Liver Disease (ALD) /Nonalcoholic Fatty Liver Disease (NAFLD) Index (ANI)

http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/alcoholic-liver-disease-nonalcoholic-fatty-liver-disease-index

The ANI is a novel scoring system that is highly accurate in distinguishing ALD from NAFLD. The ANI may be a useful tool for the frequent clinical scenarios in which it is useful to ascertain alcoholic liver injury. Short short-term abstinence does not significantly affect the performance characteristics of the ANI therefore the ANI is unlikely to be useful in detecting surreptious alcohol consumption in patients with known ALD. Other liver diseases should first be excluded before utilizing the ANI. The ANI is most accurate when the MELD Score is below 20.

Please enter values and press Calculate ANI.

AST: IU/l ALT: IU/l MCV: fL
Weight: kg/lb Height: m/in
Gender: Male
Female
ANI score:
Probability of ALD:

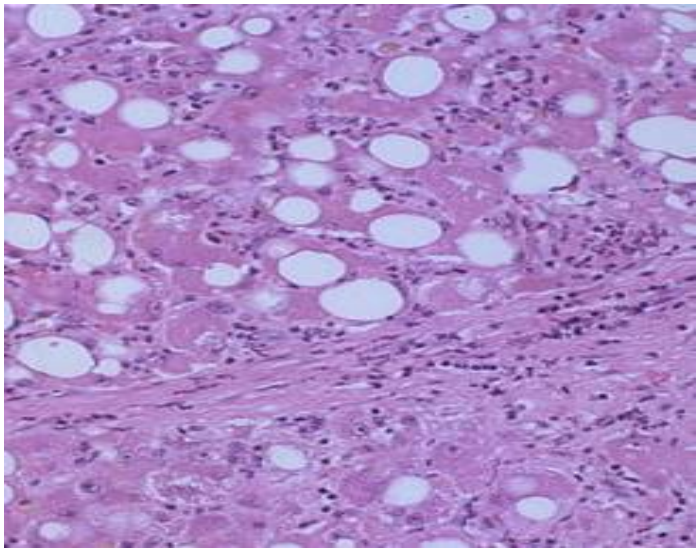
How to distinguish ALD and NAFLD? AST/ALT ratio

ASH

AST/ALT ratio >2

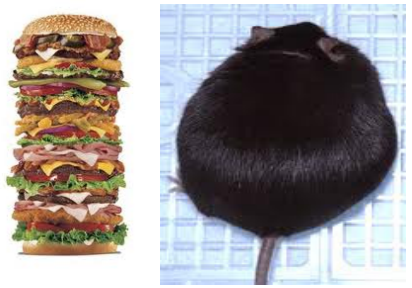
AST/ALT ratio >2

or



NASH

AST/ALT ratio <1



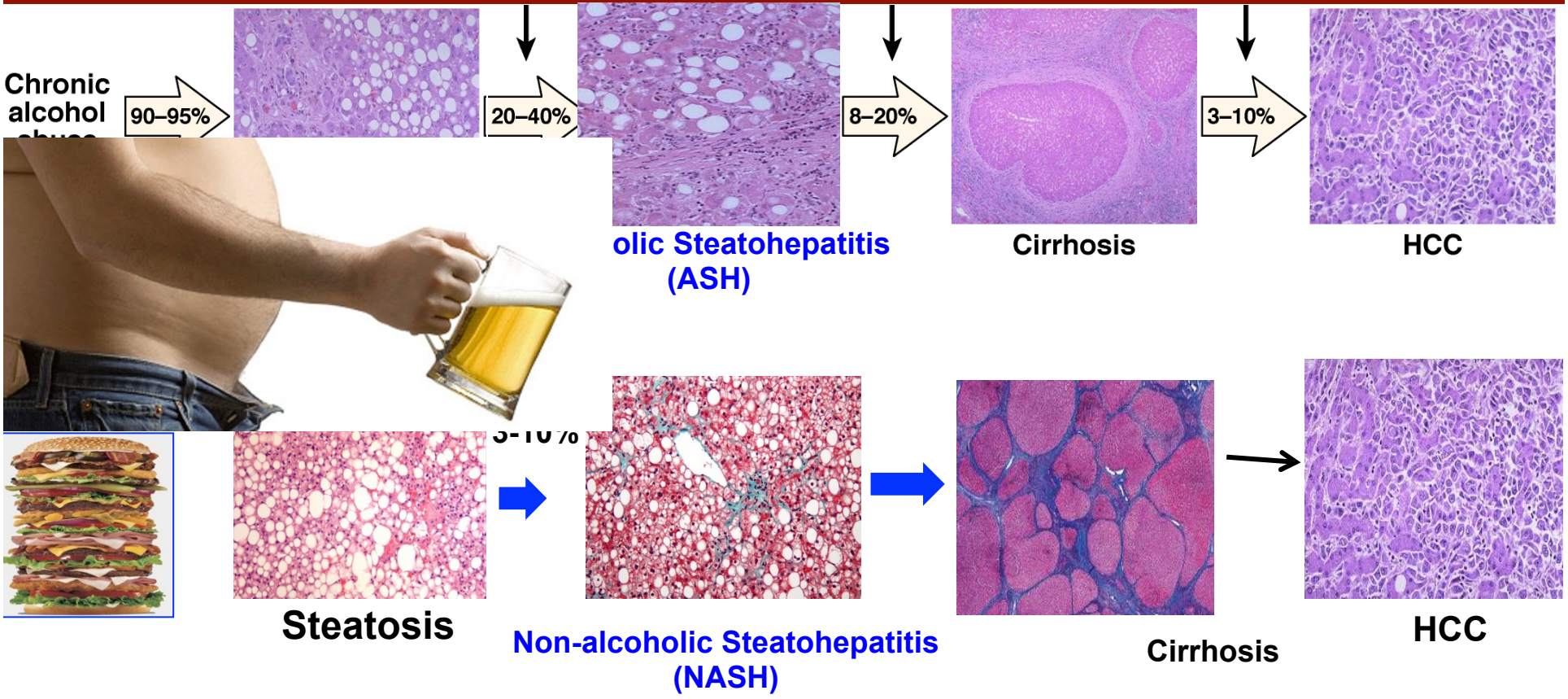
AST/ALT ratio <1

Liver mitochondrial injury
Hepatocyte injury → AST and ALT ↑

Heart and muscle mitochondrial injury → AST ↑

Hepatocyte injury → ALT and AST ↑

Spectrum of Alcoholic Liver Disease (ALD) and Non-alcoholic Fatty Liver Disease (NAFLD)



Excessive alcohol drinking exacerbates nonalcoholic fatty liver disease, cirrhosis, and liver cancer

- **Moderate alcohol drinking?**
- **Endogenous ethanol?**

Dunn et al. , Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in patients with NAFLD. J Hepatol. 2012;57:384-91.

Dunn et al., Modest wine drinking and decreased prevalence of suspected nonalcoholic fatty liver disease. Hepatology. 2008;47:1947-54.

Zhu et al.: Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. Hepatology. 2013, 57:601-9.

In NASH patients: gut alcohol-producing bacteria ↑ → blood ethanol ↑ → ethanol metabolism, oxidative stress, liver inflammation ↑ → NSAH

More studies?

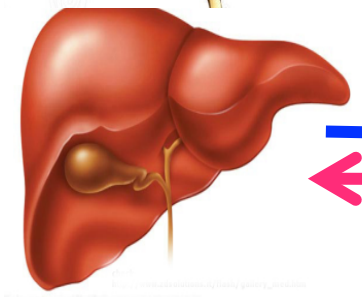
- Moderate alcohol drinking?
- Endogenous ethanol?

Therapy of Alcoholic Liver Disease (ALD)

Alcohol

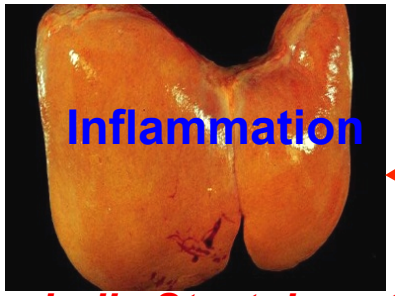
Acute (sub-acute) Alcoholic Hepatitis

Clinical syndrome: Jaundice, hepatomegaly, fever, Neutrophilia, AST: ALT ratio>2



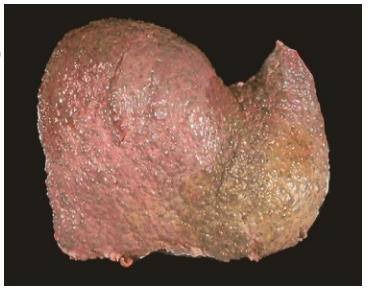
Fatty Liver

30-40%



Alcoholic Steatohepatitis (ASH)

10-20%



Cirrhosis

1. Stop drinking
2. Supporting treatment
3. There are no approved anti-fibrotic drugs.
4. Management of alcoholic cirrhosis and HCC: similar to other causes
5. Treatment of alcoholic hepatitis (AH): high mortality

   Steroid (prednisone) , Novel therapeutic targets: interleukin-22

Prednisolone for alcoholic hepatitis 1971 → 2015

Controversies in steroid treatment for alcoholic hepatitis

Mathurin P, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. *Gut* 2011;60:255-60.

di Mambro AJ, et al. In vitro steroid resistance correlates with outcome in severe alcoholic hepatitis. *Hepatology* 2011;53:1316-22.

Louvet A, et al. Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. *Gastroenterology* 2009;137:541-8.

Singal AK, Shah VH. Alcoholic hepatitis: prognostic models and treatment. *Gastroenterol Clin North Am* 2011;40:611-39.

Christensen E. Glucocorticosteroids in acute alcoholic hepatitis: the evidence of a beneficial effect is getting even weaker. *J Hepatol* 2010;53:390-1.

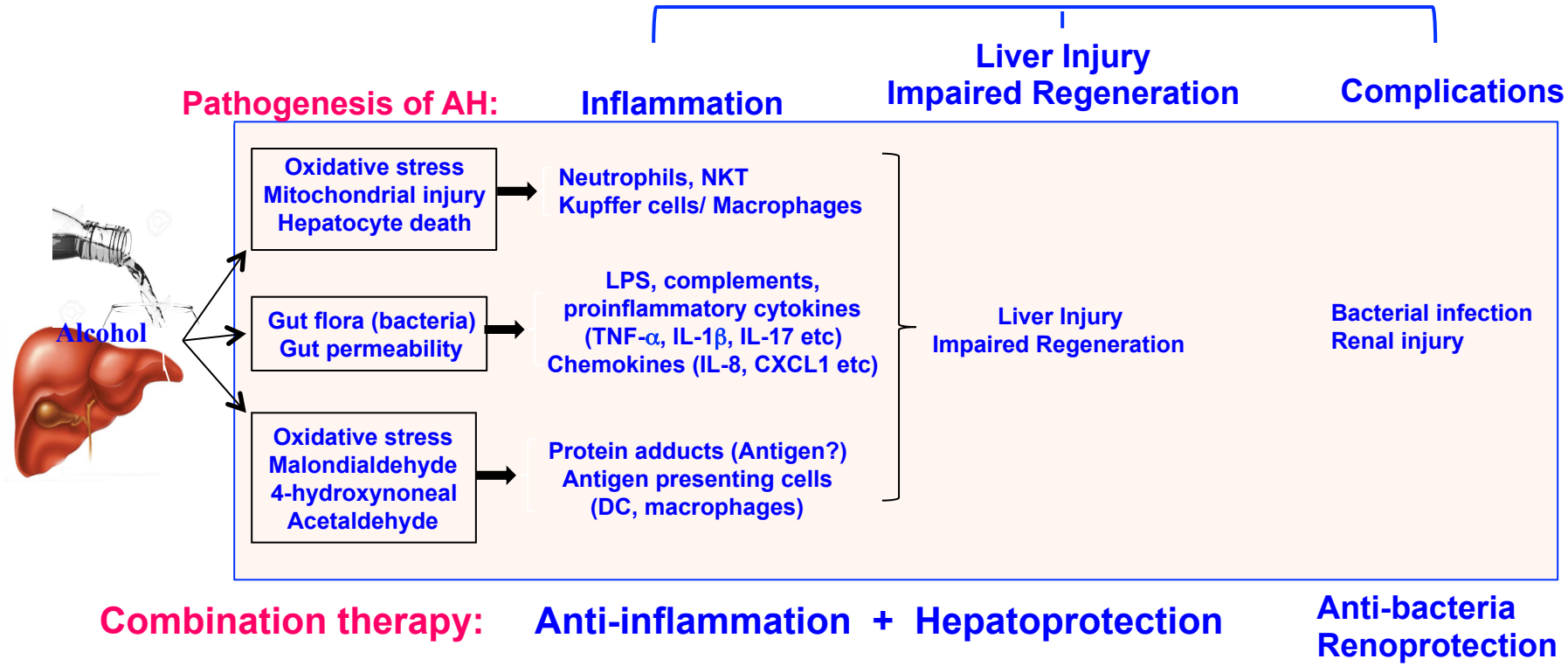
Over the years the evidence in favour of glucocorticosteroid therapy in alcoholic hepatitis has steadily decreased, and now it seems to be the time to move on to other therapies with more potential, e.g., pentoxifylline.

NIAAA supports four large consortia to conduct translational research for exploring novel therapeutic targets for alcoholic hepatitis

Combination therapy: new hope for alcoholic hepatitis (AH)?

Bin Gao, MD PhD,
Laboratory of Liver Diseases, NIAAA, NIH, Bethesda, MD, USA

Vijay Shah, MD
Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA



Key points:

Interleukin-22 is probably the only cytokine that is produced by immune cells but does target immune cells due to lack of IL-22 receptor 1 (IL-22R1) on these cells.

Interleukin-22 mainly targets epithelial cells (eg. hepatocytes), hepatic stellate cells, and some fibroblasts because of high levels of IL-22R1 on these cells.

Key functions of Interleukin-22 in the liver:

Radaeva et al. *Hepatology* 2004

Induces hepatocyte survival
Induces hepatocyte proliferation
Induces expression of anti-bacterial genes

Phase I clinical trial in healthy volunteers (finished)(Generon)
Phase IB or Phase II for alcoholic hepatitis is under consideration

Challenges for alcoholic liver disease (ALD)

1. Stop drinking, Overcoming an addiction,
2. Pathogeneses of ALD remain obscure.
3. Non-invasive markers for diagnosis of early ALD
4. There are no approved drugs for the treatment of ALD.
5. Animal models of ALD